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Associations between systemic inflammation response index and femur bone mineral density in adults

The NHANES 2005–2010, 2013–2014, and 2017–2018

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Abstract

A unique measure of inflammatory evaluation, the systemic inflammation response index (SIRI) may offer useful data for the diagnosis and risk assessment of a number of diseases. The aim of this study was to investigate the relationship between SIRI and femur bone mineral density (BMD) in US adults. The association between SIRI and femur BMD was examined using multivariate logistic regression, sensitivity analysis, and smoothing curve fitting using data from the National Health and Nutrition Examination Survey (NHANES) 2005–2010, 2013–2014, and 2017–2018. Subgroup analysis and interaction tests were employed to examine the population-level stability of this connection. This present study included 18,022 participants older than 20 years from NHANES (2005–2010, 2013–2014, and 2017–2018). The present study showed a negative association between SIRI and femur BMD (including total femur BMD, femoral neck BMD, trochanter BMD, and intertrochanter BMD). In the fully adjusted model, we found a negative association between the SIRI and total femur BMD (Beta = –0.0032, 95% CI: –0.0053 to –0.0012), a negative association between the SIRI and femoral neck BMD (Beta = –0.0025, 95% CI: –0.0045 to –0.0005), a negative association between the SIRI and trochanter BMD (Beta = –0.0032, 95% CI: –0.0050 to –0.0013), a negative association between the SIRI and intertrochanter BMD (Beta = –0.0031, 95% CI: –0.0056 to –0.0007). This negative association was more pronounced in older adults > 65 years of age. In addition, we found a U-shaped association between SIRI and femur BMD by further smoothing curve-fitting methods. SIRI was negatively associated with femur BMD in US adults, and this association was more significant in older adults over 65 years. SIRI may be a useful, convenient, and practical indicator of inflammation. Moreover, older adults with high SIRI levels are likely to have low femur BMD.

Abbreviations: BMD = bone mineral density, BMI = body mass index, HDL-C = high-density lipoprotein-cholesterol, NHANES = National Health and Nutrition Examination Survey, NLR = neutrophil-to-lymphocyte ratio, P = phosphorus, PIR = income-to-poverty ratio, PLR = platelet-to-lymphocyte ratio, PMOP = postmenopausal osteoporosis, SD = standard deviation, SII = systemic immune-inflammation index, SIRI = systemic inflammation response index.

Keywords: bone mineral density, femur, NHANES, osteoporosis, systemic inflammation response index

1. Introduction

Reduction of bone mass, degradation of the microstructure of bone tissue, and imbalance of bone homeostasis are the characteristics of osteoporosis, a systemic metabolic bone disease.[1] A complex, chronic, non-communicable disease, osteoporosis affects one-fifth of men and one-third of women over the age of 50 worldwide and increases the risk of fracture.[2,3] With the accelerated aging of the global population, the incidence of osteoporosis and osteoporotic fracture has increased

XY, XL, and CZ contributed equally to this work.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

The portions of this study involving human participants, human materials, or human data were conducted in accordance with the Declaration of Helsinki and were approved by the NCHS Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

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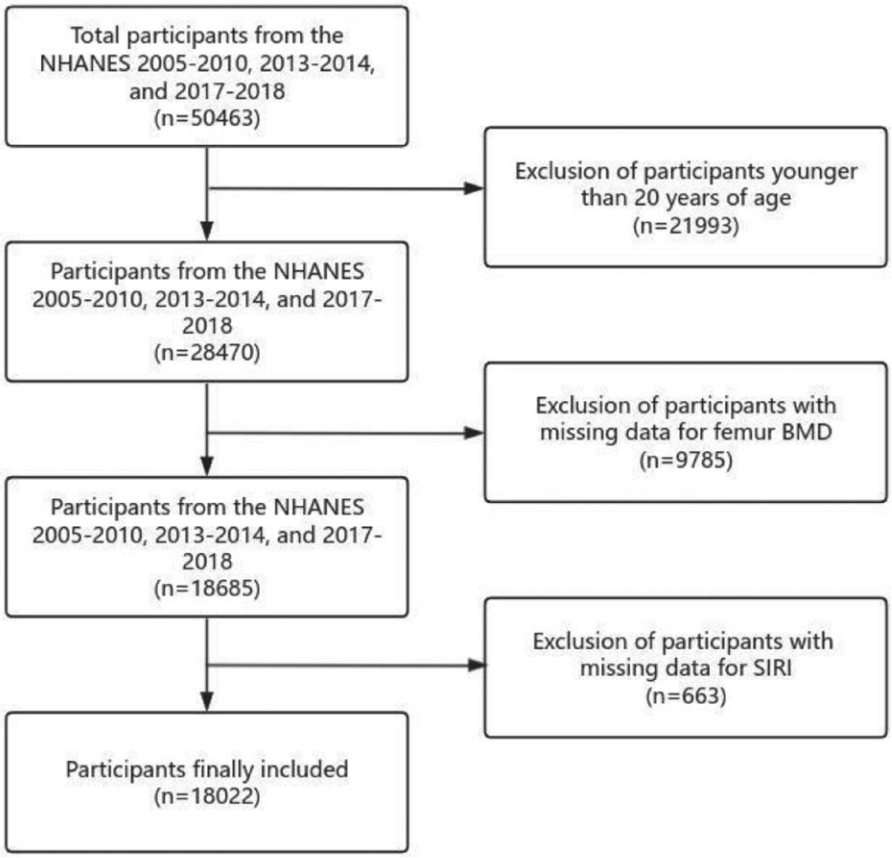

Figure 1. Flow chart of participants selection from NHANES 2005–2010, 2013–2014, and 2017–2018. NHANES = National Health and Nutrition Examination Survey.

significantly and will continue to increase significantly in the future,[4,5] and it has become an increasingly serious public health problem in various countries.[6,7] Femur bone mineral density (BMD) is a commonly used indicator for evaluating bone health and diagnosing osteoporosis, and low BMD is typically linked to a higher risk of fracture.[8,9] Therefore, the search for biomarkers associated with femur BMD is receiving increasing attention.

A number of previous studies have suggested that some indicators from immune cell counts reflecting systemic immune and inflammatory status may be associated with the risk of osteoporosis.[10–13] Related studies suggest that immune cells may have direct or indirect effects on bone cell physiologic processes.[14–16] Previous related experiments have shown that the inflammatory response can lead to differentiation or apoptosis of bone mesenchymal stem cells and osteoblasts through oxidative stress, which is associated with the pathogenesis of osteoporosis.[17,18] Systemic inflammation response index (SIRI) is a novel indicator of inflammation and immunity calculated from neutrophil counts, monocyte counts and lymphocyte counts. There is growing evidence that SIRI is a useful indicator of systemic immune and inflammatory status.

Several previous studies have shown that osteoporosis is often accompanied by the development of mild inflammation.[19–21] The association between SIRI and femur BMD has not been examined, despite pertinent studies showing that SIRI can offer useful information for the diagnosis and risk prediction of numerous diseases. As a result, this study has potential clinical value. Therefore, using information from the National Health and Nutrition Examination Survey (NHANES) 2005–2010, 2013–2014, and 2017–2018, we carried out a cross-sectional study to investigate the connection between SIRI and femur BMD.

2. Methods

2.1. Study population

The NHANES is a large, multi-stage, ongoing cross-sectional study conducted by the National Center for Health Statistics to collect accurate health-related data on the US non-institutionalized population in order to deal with emerging public health issues. The NHANES utilizes a multi-stage, probability-based stratified survey methodology that is conducted every two years, resulting in accurate and representative survey data. The present study collected data from NHANES 2005–2010, 2013–2014, and 2017–2018. We excluded 21,993 participants under the age of 20, 9785 participants without available BMD data, 663 participants with missing or incomplete SIRI data. The present study eventually included 18,022 participants (Fig. 1).

2.2. Systemic inflammation response index

SIRI is a novel, noninvasive, nonspecific biomarker of systemic inflammation based on neutrophil counts, monocyte counts, and lymphocyte counts. The SIRI for each participant was calculated using an exact formula: SIRI = neutrophil count × monocyte count/lymphocyte count. In this study, SIRI was considered a continuous variable and participants were grouped according to quartiles of SIRI for further analysis.

2.3. Femur bone mineral density

Dual-energy X-ray absorptiometry, the most extensively used low-radiation exposure technique, was used to measure femur BMD. The femur BMD that were assessed in the study included

the total femur BMD, femoral neck BMD, trochanter BMD, and intertrochanter BMD.

The femur BMD was considered as the outcome variable in this study, while the SIRI was intended to be the exposure variable.

2.4. Covariates

The covariates included demographics data, examination data, laboratory data and questionnaire data. Demographics data included age (years), gender (male, female), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other races), education level (less than high school, High school graduate/GED or equivalent, above high school), income-to-poverty ratio (PIR). Examination data included body mass index (BMI, kg/m^2). Laboratory data included blood urea nitrogen (mg/dL), total calcium (mg/dL), creatinine (Cr, mg/dL), uric acid (mg/dL), phosphorus (P, mg/dL), high-density lipoprotein-cholesterol (HDL-C, mg/dL). Questionnaire data included drinking alcohol (ever have 4/5 or more drinks every day, yes/no), smoking status (smoked at least 100 cigarettes in life, yes/no), diabetes (yes, no), hypertension (yes, no). Details of all these variables are publicly available at www.cdc.gov/nchs/nhanes/.

2.5. Statistical analysis

When it comes to continuous variables, it is represented as the mean with standard deviation (mean ± SD), while categorical parameters are presented as proportions. Using the *t* test for continuous variables and the chi-square test for categorical variables, the participant's demographics were assessed by SIRI quartile. Multivariable linear regression models were used to assess the relationship between SIRI and femur BMD. No covariates were adjusted in model 1. Gender, age, and race adjustments were made to Model 2. Model 3 was adjusted for

Table 1

Basic characteristics of participants by systemic inflammation response index among U.S. adults

	Systemic inflammation response index					
Characteristics	**Overall**	**Q1 (N = 4423)**	**Q2 (N = 4576)**	**Q3 (N = 4517)**	**Q4 (N = 4506)**	***P* value**
Age (years)	52.99 ± 16.96	50.36 ± 15.82	51.51 ± 16.39	52.84 ± 17.10	57.24 ± 17.65	<.001
Gender (%)						<.001
Male	51.15	42.32	47.29	53.66	61.21	
Female	48.85	57.68	52.71	46.34	38.79	
Race/ethnicity (%)						<.001
Mexican American	16.87	16.39	18.60	18.24	14.23	
Other Hispanic	9.07	9.47	10.29	9.08	7.41	
Non-Hispanic White	47.36	29.60	45.56	52.93	61.05	
Non-Hispanic Black	18.96	34.07	17.35	13.20	11.54	
Other races	7.74	10.47	8.20	6.55	5.77	
Education level, (%)						.019
<High school	26.27	26.86	26.22	25.75	26.28	
High school	23.62	22.22	22.60	24.44	25.21	
>High school	49.99	50.85	51.09	49.63	48.38	
Missing	0.12	0.07	0.09	0.18	0.13	
Family PIR	2.60 ± 1.56	2.58 ± 1.57	2.65 ± 1.58	2.63 ± 1.56	2.53 ± 1.53	.003
Drinking alcohol (%) (ever have 4/5 or more drinks every day)						<.001
Yes	14.99	12.10	13.77	15.45	18.60	
No	68.05	68.14	68.97	68.21	66.87	
Missing	16.96	19.76	17.26	16.34	14.53	
Smoking status (%) (smoked at least 100 cigarettes in life)						<.001
Yes	47.40	39.75	45.39	47.66	56.70	
No	52.56	60.21	54.61	52.34	43.19	
Missing	0.04	0.04	0.00	0.00	0.11	
Diabetes (%)						<.001
Yes	15.31	13.29	13.46	15.32	19.17	
No	84.62	86.66	86.50	84.59	80.74	
Missing	0.07	0.05	0.04	0.09	0.09	
Hypertension (%)						<.001
Yes	37.75	32.94	34.44	36.97	46.63	
No	62.09	66.92	65.36	62.90	53.22	
Missing	0.16	0.14	0.20	0.13	0.15	
BMI (kg/m^2)	28.36 ± 5.72	27.89 ± 5.57	28.20 ± 5.56	28.72 ± 5.82	28.61 ± 5.88	<.001
Blood urea nitrogen (mg/dL)	13.82 ± 5.92	12.68 ± 4.72	13.37 ± 5.14	13.94 ± 5.75	15.26 ± 7.41	<.001
Total calcium (mg/dL)	9.43 ± 0.37	9.43 ± 0.36	9.43 ± 0.36	9.44 ± 0.36	9.43 ± 0.38	.855
HDL-C (mg/dL)	53.18 ± 16.11	55.54 ± 16.60	53.33 ± 15.87	52.08 ± 15.70	51.81 ± 16.02	<.001
Creatinine (mg/dL)	0.92 ± 0.43	0.87 ± 0.28	0.89 ± 0.35	0.93 ± 0.51	1.00 ± 0.51	<.001
Uric acid (mg/dL)	5.48 ± 1.41	5.26 ± 1.34	5.39 ± 1.38	5.55 ± 1.37	5.71 ± 1.50	<.001
Phosphorus (mg/dL)	3.73 ± 0.56	3.75 ± 0.54	3.74 ± 0.55	3.74 ± 0.57	3.71 ± 0.58	<.001
Total femur BMD (gm/cm^2)	0.96 ± 0.16	0.97 ± 0.17	0.96 ± 0.16	0.97 ± 0.16	0.95 ± 0.16	<.001
Femoral neck BMD (gm/cm^2)	0.82 ± 0.15	0.83 ± 0.16	0.81 ± 0.15	0.82 ± 0.15	0.80 ± 0.15	<.001
Trochanter BMD (gm/cm^2)	0.72 ± 0.14	0.73 ± 0.14	0.72 ± 0.13	0.73 ± 0.14	0.72 ± 0.14	<.001
Intertrochanter BMD (gm/cm^2)	1.14 ± 0.19	1.15 ± 0.19	1.13 ± 0.19	1.14 ± 0.19	1.13 ± 0.19	<.001

Mean ± SD for continuous variables: the *P* value was calculated by the linear regression model; (%) for categorical variables: the *P* value was calculated by the chi-square test.

BMD = bone mineral density, BMI = body mass index, HDL-C = high-density lipoprotein-cholesterol, PIR = the ratio of income to poverty, Q = quartile.

age, gender, race, education level, PIR, BMI, drinking alcohol, diabetes, blood urea nitrogen, total calcium, creatinine, uric acid, phosphorus, hypertension, HDL-C, and smoking status. The trend of the linear relationship between SIRI and femur BMD was examined using a trend test following the conversion of SIRI from a continuous variable to a categorical variable (quartile). Subgroup analysis was used to investigate the association between SIRI and femur BMD in people of different gender (male, female), age (<65 years, ≥65 years), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other races), education level (less than high school, High school graduate/GED or equivalent, above high school), BMI (<18.5kg/m^2, 18.5–24.9kg/m^2, 25.0–29.9kg/m^2, 30.0–34.9kg/m^2, 35.0–39.9kg/m^2, ≥40.0kg/m^2), drinking alcohol (yes, no), smoking status (yes, no), hypertension status (yes, no), and diabetes status (yes, no), and interaction tests were used to investigate whether the associations were consistent across subgroups. To investigate the nonlinear relationship between SIRI and femur BMD, smoothing curve fitting was employed. The likelihood ratio test was used to ascertain the values of the inflection points after a nonlinear association between SIRI and femur BMD was demonstrated. R (version 4.2) or EmpowerStats (version 5.0) were used for all analyses. A statistically significant result was defined as a two-tailed *P* value less than .05.

3. Results

3.1. Baseline characteristics

This present study included 18,022 participants older than 20 years from NHANES (2005–2010, 2013–2014, and 2017–2018). The mean (SD) age of the 18,022 participants was 52.99 (16.96), of whom 51.15% were male and 48.85% were female. The mean (SD) SIRI for all participants was 1.23 (0.92), with an interquartile range of quartile 1: < 0.700; quartile 2: 0.700–1.025; quartile 3: 1.025–1.487; quartile 4: >1.487. The mean (SD) total femur BMD for all participants was 0.96 (0.16), mean (SD) femoral neck BMD was 0.82 (0.15), mean (SD) trochanter BMD was 0.72 (0.14), mean (SD) intertrochanter BMD was 1.14 (0.19). Among the four SIRI quartiles, differences with statistical significance were observed in age, gender, race, education level, family PIR, drinking alcohol status, smoking status, BMI, diabetes, hypertension, blood urea nitrogen, serum uric acid, HDL-C, creatinine, and phosphorus (all $P < .05$). Compared with the lowest SIRI quartile, participants in the increased SIRI group were significantly more likely to be male and non-Hispanic white, and to have hypertension and diabetes (all $P < .05$). In addition, participants with higher SIRI typically had higher BMI, blood urea nitrogen, creatinine, uric acid, as well as lower HDL-C (Table 1).

3.2. Association between SIRI and femur BMD

It shows the associations between SIRI and femur BMD in Table 2. In present results, it showed that a higher SIRI was associated with a lower total femur BMD, a lower femoral neck BMD, a lower trochanter BMD, a lower intertrochanter BMD.

In the total femur BMD group, it showed a significant negative association between SIRI and total femur BMD in both the crude model (Beta = −0.0065, 95% CI: −0.0090 to −0.0039) and partially adjusted model (Beta = −0.0023, 95% CI: −0.0045 to 0.0000). In the fully adjusted model, a negative association between the SIRI and total femur BMD was observed (Beta = −0.0032, 95% CI: −0.0053 to −0.0012), indicating that each unit of increased SIRI was associated with 0.0032 decreased units of total femur BMD. After SIRI was classified as quartiles, the above association remained statistically significant in both the crude model and fully adjusted model (both *P* for trend < .05). In the fully adjusted model, the mean total femur BMD of the highest SIRI quartile was 0.0106 units lower than

Table 2

Associations between systemic inflammation response index and femur bone mineral density

	Total femur BMD	Femoral neck BMD	Trochanter BMD	Intertrochanter BMD
SIRI	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
Crude model (Model 1)				
Continuous	−0.0065 (−0.0090, −0.0039)	−0.0129 (−0.0154, −0.0105)	−0.0037 (−0.0058, −0.0015)	−0.0066 (−0.0096, −0.0036)
Categories				
Quartile 1	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Quartile 2	−0.0116 (−0.0183, −0.0049)	−0.0191 (−0.0255, −0.0128)	−0.0076 (−0.0132, −0.0020)	−0.0134 (−0.0213, −0.0055)
Quartile 3	−0.0033 (−0.0100, 0.0035)	−0.0147 (−0.0211, −0.0083)	−0.0003 (−0.0059, 0.0053)	−0.0036 (−0.0115, 0.0043)
Quartile 4	−0.0167 (−0.0234, −0.0100)	−0.0359 (−0.0423, −0.0295)	−0.0103 (−0.0159, −0.0047)	−0.0167 (−0.0246, −0.0088)
P for trend	<.0001	<.0001	.0032	.0008
Minimally adjusted model (Model 2)				
Continuous	−0.0023 (−0.0045, 0.0000)	−0.0014 (−0.0035, 0.0007)	−0.0027 (−0.0047, −0.0007)	−0.0020 (−0.0047, 0.0007)
Categories				
Quartile 1	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Quartile 2	−0.0027 (−0.0085, 0.0030)	−0.0042 (−0.0096, 0.0011)	−0.0027 (−0.0077, 0.0023)	−0.0034 (−0.0103, 0.0035)
Quartile 3	0.0049 (−0.0009, 0.0108)	0.0046 (−0.0008, 0.0100)	0.0027 (−0.0024, 0.0078)	0.0057 (−0.0013, 0.0127)
Quartile 4	−0.0020 (−0.0080, 0.0040)	−0.0016 (−0.0071, 0.0040)	−0.0053 (−0.0105, −0.0001)	−0.0002 (−0.0073, 0.0070)
P for trend	.7802	.9325	.0785	.6752
Fully adjusted model (Model 3)				
Continuous	−0.0032 (−0.0053, −0.0012)	−0.0025 (−0.0045, −0.0005)	−0.0032 (−0.0050, −0.0013)	−0.0031 (−0.0056, −0.0007)
Categories				
Quartile 1	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Quartile 2	−0.0079 (−0.0131, −0.0027)	−0.0085 (−0.0135, −0.0036)	−0.0064 (−0.0111, −0.0018)	−0.0095 (−0.0157, −0.0033)
Quartile 3	−0.0058 (−0.0111, −0.0005)	−0.0044 (−0.0094, 0.0007)	−0.0048 (−0.0096, −0.0001)	−0.0070 (−0.0133, −0.0006)
Quartile 4	−0.0106 (−0.0161, −0.0052)	−0.0092 (−0.0144, −0.0040)	−0.0110 (−0.0158, −0.0061)	−0.0103 (−0.0168, −0.0038)
P for trend	.0013	.0078	<.0001	.0158

Model 1: no covariates were adjusted. Model 2: age, gender, and race were adjusted. Model 3: age, gender, race, education level, PIR, BMI, drinking alcohol, diabetes, blood urea nitrogen, total calcium, creatinine, uric acid, phosphorus, hypertension, HDL-C, and smoking status were adjusted.

BMD = bone mineral density, BMI = body mass index, HDL-C = high-density lipoprotein-cholesterol, PIR = the ratio of income to poverty, SIRI = systemic inflammation response index.

that of the lowest quartile (Beta = −0.0106, 95% CI: −0.0161 to −0.0052) (Table 2).

For femoral neck BMD, the present study found a negative association between SIRI and femoral neck BMD in the crude model (Beta = −0.0129, 95% CI: −0.0154 to −0.0105) with statistical significance, but this association became insignificant in the partially adjusted model (Beta = −0.0014, 95% CI: −0.0035 to 0.0007). After full adjustment, a negative association between the SIRI and femoral neck BMD was observed (Beta = −0.0025, 95% CI: −0.0045 to −0.0005), indicating that each unit of increased SIRI was associated with 0.0025 decreased units of femoral neck BMD. After SIRI was treated as quartiles, the association remained statistically significant in both the crude model and fully adjusted model (both *P* for trend < 0.05). In the fully adjusted model, the mean femoral neck BMD of the highest SIRI quartile was 0.0092 units lower than that of the lowest quartile (Beta = −0.0092, 95% CI: −0.0144 to −0.0040) (Table 2).

In the trochanter BMD group, the results showed a significant negative association between SIRI and trochanter BMD in both the crude model (Beta = −0.0037, 95% CI: −0.0058 to −0.0015) and partially adjusted model (Beta = −0.0027, 95% CI: −0.0047 to −0.0007). In the fully adjusted model, a negative association between the SIRI and trochanter BMD was observed (Beta = −0.0032, 95% CI: −0.0050 to −0.0013), indicating that each unit of increased SIRI was associated with 0.0032 decreased units of trochanter BMD. After SIRI was classified as quartiles, the above association remained statistically significant in both the crude model and fully adjusted model (both *P* for trend < .05). In the fully adjusted model, the mean trochanter BMD of the highest SIRI quartile was 0.0110 units lower than that of the lowest quartile (Beta = −0.0110, 95% CI: −0.0158 to −0.0061) (Table 2).

For intertrochanter BMD, the present study found a negative association between SIRI and intertrochanter BMD in the crude model (Beta = −0.0066, 95% CI: −0.0096 to −0.0036) with statistical significance, but this association became insignificant in the partially adjusted model (Beta = −0.0020, 95% CI: −0.0047 to 0.0007). After full adjustment, a negative association between the SIRI and intertrochanter BMD was observed (Beta = −0.0031, 95% CI: −0.0056 to −0.0007), indicating that each unit of increased SIRI was associated with 0.0031 decreased units of intertrochanter BMD. After SIRI was treated as quartiles, the association remained statistically significant in the crude model and fully adjusted model (both *P* for trend < .05). In the fully adjusted model, the mean intertrochanter BMD of the highest SIRI quartile was 0.0103 units lower than that of the lowest quartile (Beta = −0.0103, 95% CI: −0.0168 to −0.0038) (Table 2).

3.3. Smooth curve fitting and threshold effect analysis

The smooth curve fit revealed a U-shaped association between SIRI and femur BMD (Figs. 2–5).

In the total femur BMD group, a breakpoint (K) of 11.8 was determined through threshold effect analysis. To the left of the breakpoint, a negative association between SIRI and total femur BMD was observed (Beta = −0.0042, 95% CI: −0.0064 to −0.0020) with statistical significance. But it became an insignificant positive association between SIRI and total femur BMD to the right of the breakpoint (Beta = 0.0119, 95% CI: −0.0006 to 0.0245). The log-likelihood ratio test *P* value was .016 (Table 3).

For femoral neck BMD, we calculated that the breakpoint (K) was 10.0 through threshold effect analysis. To the left of the breakpoint, a negative association between SIRI and femoral neck BMD was observed (Beta = −0.0035, 95% CI: −0.0057 to −0.0014). To the right of the breakpoint, a positive correlation between SIRI and femoral neck BMD was observed (Beta = 0.0102, 95% CI: 0.0003–0.0201). The log-likelihood ratio test *P* value was .011 (Table 3).

In the trochanter BMD group, a breakpoint (K) of 10.0 was determined through threshold effect analysis. To the left of the breakpoint, a negative association between SIRI and trochanter BMD was observed (Beta = −0.0043, 95% CI: −0.0063 to −0.0023). But it became a significant positive association between SIRI and trochanter BMD to the right of the breakpoint (Beta = 0.0103, 95% CI: 0.0010–0.0196). The log-likelihood ratio test *P* value was .004 (Table 3).

For intertrochanter BMD, we calculated that the breakpoint (K) was 12.0 through threshold effect analysis. To the left of the breakpoint, a negative association between SIRI and intertrochanter BMD was observed (Beta = −0.0040, 95% CI: −0.0066 to −0.0014). To the right of the breakpoint, an insignificant positive correlation between SIRI and intertrochanter BMD was observed (Beta = 0.0112, 95% CI: −0.0041 to 0.0265). The log-likelihood ratio test *P* value was .063 (Table 3).

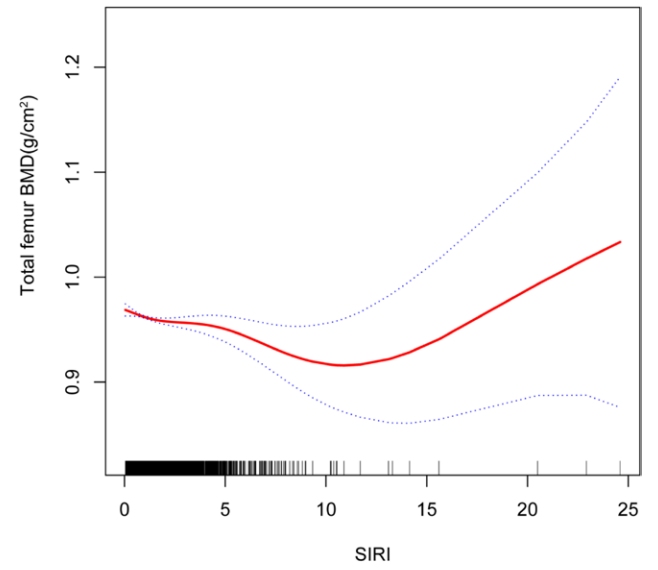

Figure 2. The nonlinear associations between SIRI and total femur BMD. BMD = bone mineral density, SIRI = systemic inflammation response index.

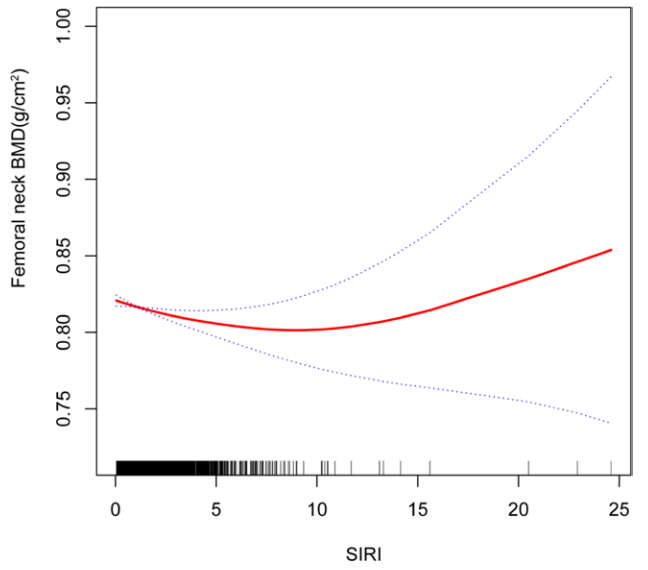

Figure 3. The nonlinear associations between SIRI and femoral neck BMD. BMD = bone mineral density, SIRI = systemic inflammation response index.

3.4. Subgroup analyses

In order to determine whether the relationship between SIRI and femur BMD was consistent in the general population and to identify any potential different population settings, the current study performed subgroup analysis and interaction tests stratified by age, gender, race, education level, BMI, drinking alcohol, diabetes, hypertension, and smoking status (Table 4). In the four groups of femur BMD, the results showed that the association between SIRI and femur BMD was significantly different between age subgroups (all *P* for interaction < .05). In four groups of older adults greater than or equal to 65 years, the association between SIRI and femur BMD was a significant negative association, but it became a non-significant negative association among those younger than 65 years. In the total femur BMD group and intertrochanter BMD group, the results showed that the association between SIRI and femur BMD was significantly different between BMI subgroups (both *P* for interaction < .05). In the femoral neck BMD group and trochanter BMD group, the results showed that the association between SIRI and femur BMD was significantly different between hypertension subgroups (both *P* for interaction < .05). In both groups of participants with hypertension, the association between SIRI and femur BMD was a significant negative association, but it became a non-significant negative association among those who did not have hypertension.

4. Discussion

A total of 18,022 participants older than 20 years were included in this cross-sectional study, which showed a negative association between SIRI and femur BMD (including total femur BMD, femoral neck BMD, trochanter BMD, and intertrochanter BMD). When SIRI was transformed into a categorical variable, femur BMD was higher in the quartile with the lowest SIRI than in the remaining quartiles. By further smoothing curve-fitting methods, we found a U-shaped association between SIRI and femur BMD (including total femur BMD, femoral neck BMD, trochanter BMD, and intertrochanter BMD). Subgroup analyses showed that age altered the association between SIRI and femur BMD in all four groups of femur BMD, with a significant negative association between SIRI and femur BMD in participants over 65 years, and a change to a non-significant negative association between SIRI and femur BMD in participants under 65 years. In addition, in the total femur BMD group and the intertrochanter BMD group, the results showed that the association between SIRI and femur BMD differed significantly between the BMI subgroups. In the femoral neck BMD group and trochanter BMD group, the results showed that the association between SIRI and femur BMD was significantly different between the hypertension subgroups.

The study was based on data from the US non-institutionalized population, but there have been a number of previous studies of the relationship between BMD and some immuno-inflammatory indicators in other countries or ethnic groups. Lee et al[11] found a negative association between quartiles of neutrophil-to-lymphocyte ratio (NLR) and the mean of lumbar BMD in Korean postmenopausal women in a study of 407 postmenopausal women. Yolaçan et al[22] retrospectively evaluated 527 postmenopausal Turkish women and showed that NLR, platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio and systemic immune-inflammation index

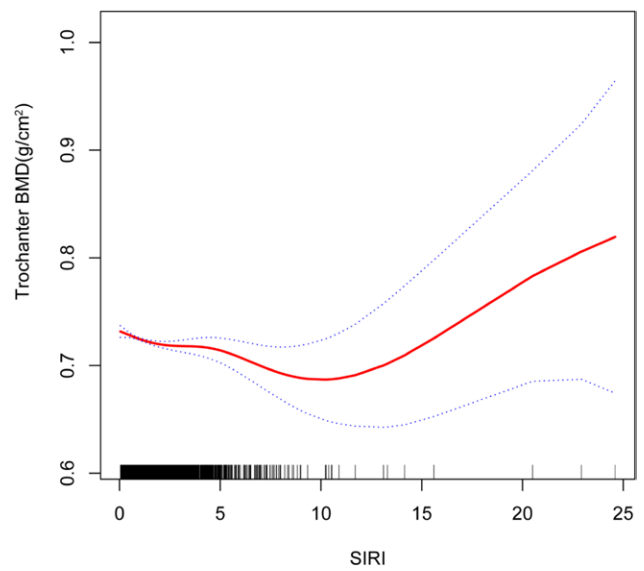

Figure 4. The nonlinear associations between SIRI and trochanter BMD. BMD = bone mineral density, SIRI = systemic inflammation response index.

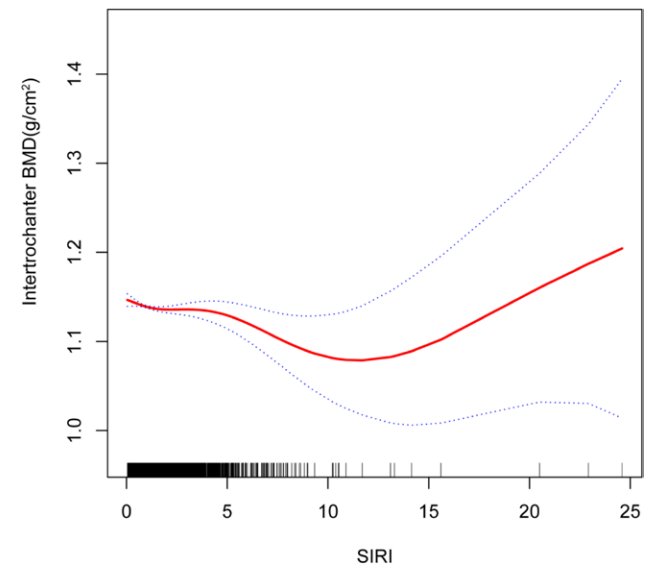

Figure 5. The nonlinear associations between SIRI and intertrochanter BMD. BMD = bone mineral density, SIRI = systemic inflammation response index.

Table 3

threshold effect analysis of the association between SIRI and femur BMD

	Total femur BMD [β (95% CI)]	Femoral neck BMD [β (95% CI)]	Trochanter BMD [β (95% CI)]	Intertrochanter BMD [β (95% CI)]
Breakpoint (K)	11.8	10.0	10.0	12.0
<K, effect 1	−0.0042 (−0.0064, −0.0020)	−0.0035 (−0.0057, −0.0014)	−0.0043 (−0.0063, −0.0023)	−0.0040 (−0.0066, −0.0014)
>K, effect 2	0.0119 (−0.0006, 0.0245)	0.0102 (0.0003, 0.0201)	0.0103 (0.0010, 0.0196)	0.0112 (−0.0041, 0.0265)
Logarithmic likelihood ratio test *P* value	.016	.011	.004	.063

Age, gender, race, education level, PIR, BMI, drinking alcohol, diabetes, blood urea nitrogen, total calcium, creatinine, uric acid, phosphorus, hypertension, HDL-C, and smoking status were adjusted.
BMD = bone mineral density, BMI = body mass index, HDL-C = high-density lipoprotein-cholesterol, PIR = the ratio of income to poverty, SIRI = systemic inflammation response index.

Table 4

Subgroup analysis of the association between SIRI and femur BMD

Subgroup	Total femur BMD [β (95% CI)]	*P* for interaction	Femoral neck BMD [β (95% CI)]	*P* for interaction	Trochanter BMD [β (95% CI)]	*P* for interaction	Intertrochanter BMD [β (95% CI)]	*P* for interaction
Gender		.4154		.7218		.1657		.6878
Male	−0.0047 (−0.0072, −0.0022)		−0.0028 (−0.0052, −0.0004)		−0.0049 (−0.0071, −0.0027)		−0.0044 (−0.0074, −0.0014)	
Female	−0.0029 (−0.0065, 0.0007)		−0.0035 (−0.0070, −0.0001)		−0.0021 (−0.0054, 0.0011)		−0.0033 (−0.0076, 0.0010)	
Age		.0048		.0190		.0049		.0054
<65 years	−0.0018 (−0.0046, 0.0010)		−0.0020 (−0.0048, 0.0007)		−0.0018 (−0.0043, 0.0006)		−0.0011 (−0.0044, 0.0022)	
≥65 years	−0.0080 (−0.0113, −0.0047)		−0.0071 (−0.0104, −0.0039)		−0.0073 (−0.0102, −0.0044)		−0.0083 (−0.0123, −0.0044)	
Race/ethnicity		.0679		.1814		.1555		.0912
Mexican American	0.0035 (−0.0020, 0.0090)		0.0018 (−0.0034, 0.0070)		0.0018 (−0.0031, 0.0067)		0.0053 (−0.0013, 0.0118)	
Other Hispanic	−0.0097 (−0.0186, −0.0008)		−0.0055 (−0.0140, 0.0030)		−0.0095 (−0.0175, −0.0015)		−0.0096 (−0.0202, 0.0011)	
Non-Hispanic White	−0.0036 (−0.0062, −0.0009)		−0.0026 (−0.0052, −0.0001)		−0.0035 (−0.0059, −0.0011)		−0.0033 (−0.0065, −0.0001)	
Non-Hispanic Black	−0.0056 (−0.0111, −0.0001)		−0.0067 (−0.0120, −0.0014)		−0.0044 (−0.0094, 0.0005)		−0.0048 (−0.0114, 0.0018)	
Other races	−0.0018 (−0.0095, 0.0059)		0.0006 (−0.0067, 0.0080)		−0.0029 (−0.0098, 0.0040)		−0.0041 (−0.0133, 0.0050)	
Education level		.3474		.0894		.2237		.7270
<High school	−0.0032 (−0.0073, 0.0009)		−0.0026 (−0.0065, 0.0013)		−0.0041 (−0.0078, −0.0004)		−0.0024 (−0.0073, 0.0025)	
High school	−0.0055 (−0.0095, −0.0014)		−0.0059 (−0.0097, −0.0020)		−0.0052 (−0.0089, −0.0016)		−0.0045 (−0.0094, 0.0003)	
>High school	−0.0018 (−0.0047, 0.0011)		−0.0005 (−0.0033, 0.0023)		−0.0015 (−0.0042, 0.0011)		−0.0022 (−0.0057, 0.0013)	
BMI		.0380		.8713		.1527		.0035
<18.5 kg/m^2	0.0111 (−0.0076, 0.0298)		0.0027 (−0.0152, 0.0206)		0.0119 (−0.0048, 0.0287)		0.0143 (−0.0080, 0.0367)	
18.5-24.9 kg/m^2	−0.0052 (−0.0090, −0.0015)		−0.0019 (−0.0055, 0.0016)		−0.0036 (−0.0070, −0.0003)		−0.0073 (−0.0117, −0.0028)	
25.0-29.9 kg/m^2	−0.0031 (−0.0065, 0.0002)		−0.0026 (−0.0058, 0.0006)		−0.0035 (−0.0065, −0.0005)		−0.0025 (−0.0065, 0.0016)	
30.0–34.9 kg/m^2	−0.0039 (−0.0085, 0.0007)		−0.0043 (−0.0087, 0.0001)		−0.0042 (−0.0083, −0.0001)		−0.0030 (−0.0085, 0.0025)	
35.0–39.9 kg/m^2	0.0085 (0.0003, 0.0168)		0.0001 (−0.0078, 0.0080)		0.0045 (−0.0028, 0.0119)		0.0135 (0.0037, 0.0233)	
≥40.0 kg/m^2	0.0012 (−0.0115, 0.0138)		0.0013 (−0.0108, 0.0134)		0.0007 (−0.0107, 0.0120)		0.0037 (−0.0115, 0.0188)	
Drinking alcohol (ever have 4/5 or more drinks every day)		.6179		.2403		.1169		.7509
Yes	−0.0055 (−0.0106, −0.0003)		−0.0062 (−0.0111, −0.0012)		−0.0075 (−0.0121, −0.0028)		−0.0032 (−0.0093, 0.0030)	
No	−0.0040 (−0.0065, −0.0015)		−0.0029 (−0.0053, −0.0005)		−0.0034 (−0.0056, −0.0011)		−0.0043 (−0.0073, −0.0013)	
Smoking status (smoked at least 100 cigarettes in life)		.2583		.1183		.1140		.6494
Yes	−0.0042 (−0.0068, −0.0015)		−0.0038 (−0.0063, −0.0012)		−0.0044 (−0.0068, −0.0020)		−0.0035 (−0.0067, −0.0003)	
No	−0.0018 (−0.0050, 0.0014)		−0.0006 (−0.0037, 0.0024)		−0.0014 (−0.0043, 0.0014)		−0.0024 (−0.0062, 0.0014)	
Diabetes (%)		.4983		.4963		.7633		.4824
Yes	−0.0018 (−0.0064, 0.0029)		−0.0010 (−0.0055, 0.0034)		−0.0026 (−0.0067, 0.0016)		−0.0013 (−0.0069, 0.0042)	
No	−0.0036 (−0.0059, −0.0013)		−0.0028 (−0.0050, −0.0006)		−0.0033 (−0.0054, −0.0012)		−0.0035 (−0.0063, −0.0008)	
Hypertension		.0621		.0496		.0434		.0947
Yes	−0.0055 (−0.0084, −0.0027)		−0.0048 (−0.0075, −0.0021)		−0.0054 (−0.0079, −0.0028)		−0.0055 (−0.0089, −0.0021)	
No	−0.0016 (−0.0046, 0.0013)		−0.0009 (−0.0037, 0.0020)		−0.0016 (−0.0043, 0.0011)		−0.0013 (−0.0049, 0.0022)	

Age, gender, race, education level, PIR, BMI, drinking alcohol, diabetes, blood urea nitrogen, total calcium, creatinine, uric acid, phosphorus, hypertension, HDL-C, and smoking status were adjusted.

BMD = bone mineral density, BMI = body mass index, HDL-C = high-density lipoprotein-cholesterol, PIR = the ratio of income to poverty, SIRI = systemic inflammation response index.

(SII) values were inversely correlated with the change in BMD in postmenopausal Turkish women. A retrospective study from Suzhou, China, found a correlation between inflammatory markers in peripheral blood and postmenopausal osteoporosis (PMOP), with levels increasing with decreasing BMD.[23] In addition, this study also found that SII had a good predictive value for PMOP, which was supported by the results of Du et al.[13] Several previous studies and the present study have examined the relationship between BMD and some immuno-inflammatory indicators, and have produced similar results. Synthesizing the findings of previous studies and those of the present study, we found that the relationship between immuno-inflammatory indicators and BMD may have some similarity, generalization, and generalizability across countries and ethnic groups.

As far as we are aware, this is the first investigation into the connection between femur BMD and SIRI in adults. Some previous studies have been done on the relationship between BMD and some immuno-inflammatory indicators. Liu W et al found that the levels of inflammatory indicators C-reactive protein and NLR were risk factors for bone loss in postmenopausal women after a study of 269 postmenopausal women.[24] Du et al conducted a cross-sectional study that recruited 413 postmenopausal women who had never received postmenopausal hormone therapy and observed a significant negative association between SII and BMD with or without adjusting for covariates, while NLR was negatively correlated with BMD only before adjusting for covariates.[13] In addition, Huang et al also found that NLR levels were strongly associated with BMD in a survey of 233 postmenopausal women without diabetes.[10] A meta-analysis showed that NLR and PLR are associated with osteoporosis and are potential targets for osteoporosis screening.[25] Fang et al[26] conducted a prospective cohort study, which demonstrated that the inflammatory index SII can be a good indicator for the diagnosis of PMOP. Similar to the results of previous studies, the present study found that the complex inflammatory immunity index SIRI was negatively correlated with femur BMD. This is because the composite indexes in these studies and the present study were derived from immune cells in routine blood tests. Each of these composite indexes can reflect inflammation in the body, and inflammatory conditions have been shown to adversely affect bone metabolism.[27] Unlike the NLR, SII, and PLR, the SIRI contains data on monocyte counts. Peripheral blood monocytes are classic indicators of inflammation, and peripheral blood monocytes are directly involved in osteoclast genesis. RANK and CCR6 expressed on monocytes are targets for the regulation of bone resorption in osteoporosis.[28] Previously reported that under suitable stimulation conditions, monocytes/macrophages can differentiate into osteoclasts.[29]

Although no study has yet elucidated the specific mechanisms underlying the association between SIRI and femur BMD, the interpretation of our findings may involve interactions between immune cells and bone cells. There is growing evidence that activated neutrophils appear to be involved in the development of bone loss by directly or indirectly inducing osteoclast formation under inflammatory conditions.[30–34] Neutrophils express a variety of mediators that favor osteoclastic bone resorption, including IFNγ, IL-6, and receptor-activator of NF-κB ligand.[19] It is well known that blood monocytes differentiate to form macrophages after penetrating blood vessels. Macrophages can have an effect on osteoblasts through their polarization profile and secreted paracrine factors.[19] In addition, it has been suggested that macrophages may drive osteoclast differentiation in the absence of estrogen.[19] Previous studies have shown that T_h17 cells are increasingly found in the bone marrow of ovariectomy mice,[35] and that T_h17 cells in the bone marrow increase the recruitment of inflammatory monocytes to the bone marrow as osteoclast precursor cells.[36] Relevant studies have shown that T_h1 cells can be polarized by IL-12 and secrete TNFα, which increases osteoblasts apoptosis and indirectly stimulates osteoclastogenesis through receptor-activator of NF-κB ligand production by B cells.[16,37] In addition, B cells can lead to increased proliferation of osteoclast progenitors through secreted granulocyte colony stimulating factor.[38] Therefore, the relationship between SIRI and femur BMD may be explained by the interaction between neutrophils, monocytes, and lymphocytes with osteoblasts and osteoclasts.

The results of the subgroup analyses showed age differences in the relationship between SIRI and femur BMD. Previous studies have shown that age is a factor that influences BMD.[39] In addition, the decline in estrogen levels in postmenopausal women can lead to bone loss. However, estrogen deficiency are not the only factor that can cause bone density to decline, as aging itself has been linked to a chronic inflammatory status called "inflamm-aging."[40] These theories go some way to explaining the association between age-altered SIRI and femur BMD. However, further studies are needed to fully elucidate this mechanism.

SIRI is a novel composite index that reflects the immune and inflammatory status of the body. SIRI is calculated based on neutrophil count, monocyte count, and lymphocyte count, which can be readily obtained from routine blood tests. SIRI not only contains a rich variety of immune and inflammatory parameters, but also is simple and economical to obtain. Therefore, SIRI has a high research prospect. Currently, SIRI is mostly used to predict the prognosis of stroke and its complications.[41–44] In addition, some studies have shown that SIRI has attracted attention because it can be used to predict the severity and prognosis of cardiovascular diseases.[45,46]

The findings of this study may provide ideas for future clinical and research experiments. First, the sample size of this study was large and the participants were nationally representative. Second, in order to assess the relationship between SIRI and femur BMD more comprehensively, this study simultaneously assessed the relationship between SIRI and total femur BMD, femoral neck BMD, trochanter BMD, and intertrochanter BMD, which is the first study to explore the relationship between SIRI and femur BMD in adults. Third, this study adjusted for confounding covariates to ensure the reliability of the results of this study. Finally, we performed subgroup analyses and smoothed curve fitting to make the findings more comprehensive and complete. Of course, this study has some limitations. First, due to the cross-sectional design of this study, the causal relationship between SIRI and femur BMD could not be determined. Second, although this study considered multiple confounding covariates, it still could not exclude the effects of all potential confounders. Finally, we were unable to incorporate data on all covariates influencing femur BMD, immune and inflammatory levels because of database limitations.

5. Conclusion

In summary, our study found that SIRI was negatively associated with femur BMD, and this association was more significant in older adults over 65 years. The SIRI may have potential value in the clinical forecast of femur BMD levels.

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